REMARKS

I. Claim Status:

Claims 4-15 are pending and stand rejected. Claims 1, 2, 6 and 16-26 have been canceled previously without prejudice. Claim 4 has been amended as described more fully herein. Support for the amendment to claim 4 is found in the Specification at pg. 6, lines 16-18, and more generally throughout the Specification. Claim 27 is new and recites the same elements as claim 15 except the new claim depends from claim 4 rather than claim 11. No new subject matter has been added by the amendments. Entry and consideration are respectfully requested.

II. Claim Objections:

Claim 14 is objected to for use of the parenthetical phrase, "word line." Claim 14 has been amended to recite "or word line" as an alternative description of "row." Accordingly, reconsideration and removal of the objection to claim 14 are respectfully requested.

III. Rejections under 35 U.S.C. § 103(a):

Claims 4, 5, 7-11 and 15 stand rejected under § 103(a) as being obvious over Xu et al. in view of Sugihara (US 6,132,683). Claim 4, as amended, is not rendered obvious over Xu et al. in view of Sugihara.

Xu et al. discloses a pair of microelectrodes in each assay well. Each microelectrode comprises a series of filaments having circular shapes formed in the filaments. The filaments of each microelectrode occupy the same plane and alternate with filaments of the other microelectrode along the plane. Each microelectrode is coupled to a separate bus and a separate connection pad. One of

the microelectrodes is configured as a driving electrode to generate an electric field within the well. The other microelectrode is operated as a sensing electrode to measure a change in impedance produced by cell(s) on the substrate.

Applicants' invention as claimed, recites a single array of individually driven microelectrodes dedicated to deliver current/voltage to the array region occupied by the array. Each microelectrode is adapted for connection to a single cell. All microelectrodes of the single array are located in a specific array region and are ***dedicated to deliver exclusively current/voltage*** to the array region to perform cell-specific electroporation.

Applicants' invention ***does not*** include a second array of individually driven microelectrodes and none of the microelectrodes present in the array region are dedicated to function as sensing microelectrodes to sense impedance changes. Such a microelectrode configuration is conceptually, structurally and functionally incompatible with an electroporation array configured to perform the exclusive function of imparting an electric field to stimulate electroporation. For all these reasons, Xu et al. does not show or suggest Applicants' claimed invention, and, in fact, teaches away from the claimed invention.

Sugihara does not fill the deficiencies of Xu et al. Sugihara et al. discloses a cell potential measuring electrode assembly that employs reference electrodes separated from other electrodes used to take impedance measurements. The reference electrodes are not introduced to the cell cultures being measured thereby reducing noise and allowing for more precise measurements. [2:35-62]. It is noteworthy that Sugihara et al. is not directed to an assembly for use in cell electroporation.

Sugihara et al. does not disclose, or even suggest, a single planar array of

microelectrodes located in a specific array region with each microelectrode individually driven and adapted to connect to single cell. Sugihara further fails to show or suggest microelectrodes of the planar array configured to exclusively deliver current/voltage to the array region. To the contrary, Sugihara et al. discloses *measuring* cell potentials using all the microelectrodes. [2:64-67]. Absent any teaching, suggestion, or motivation to dedicate individual microelectrodes to a single cell and to configure the microelectrodes to deliver exclusively, current/voltage so as to perform electroporation of the individual cell, Sugihara et al. does not render claim 4 obvious alone, or in combination with Xu et al. Accordingly, for all the foregoing reasons, Applicants respectfully request reconsideration and removal of the rejection of claim 4 under § 103(a).

Claims 5, 7-11 and 15 depend, directly or ultimately, from claim 4 and are allowable for the same reasons given for the allowability of claim 4. Accordingly, reconsideration and removal of the rejection of claims 5, 7-11 and 15 under § 103(a) are respectfully requested.

Claims 4, 5, 7-11 and 15 stand rejected as being obvious over Xu et al. in view of Sugihara (US 6,132,683) and Johnson (US 7,521,224). Claim 4, as amended, is not rendered obvious over Xu et al. in view of Sugihara and Johnson.

Xu et al. discloses a pair of microelectrodes in each assay well. Each microelectrode comprises a series of filaments having circular shapes formed in the filaments. The filaments of each microelectrode occupy the same plane and alternate with filaments of the other microelectrode along the plane. Each microelectrode is coupled to a separate bus and a separate connection pad. One of the microelectrodes is configured as a driving electrode to generate an electric field within the well. The other microelectrode is operated as a sensing electrode to

measure a change in impedance produced by cell(s) on the substrate.

Applicants' invention as claimed, recites a single array of individually driven microelectrodes dedicated to deliver current/voltage to the array region occupied by the array. Each microelectrode is adapted for connection to a single cell. All microelectrodes of the single array are located in a specific array region and are ***dedicated to deliver exclusively current/voltage*** to the array region to perform cell-specific electroporation.

Applicants' invention ***does not*** include a second array of individually driven microelectrodes and none of the microelectrodes present in the array region are dedicated to function as sensing microelectrodes to sense impedance changes. Such a microelectrode configuration is conceptually, structurally and functionally incompatible with an electroporation array configured to perform the exclusive function of imparting an electric field to stimulate electroporation. For all these reasons, Xu et al. does not show or suggest Applicants' claimed invention, and, in fact, teaches away from the claimed invention.

Sugihara does not fill the deficiencies of Xu et al. Sugihara et al. discloses a cell potential measuring electrode assembly that employs reference electrodes separated from other electrodes used to take impedance measurements. The reference electrodes are not introduced to the cell cultures being measured thereby reducing noise and allowing for more precise measurements. [2:35-62]. Again, it is noteworthy that Sugihara et al. is not directed to an assembly for use in cell electroporation.

Sugihara et al. does not disclose, or even suggest, a single planar array of microelectrodes located in a specific array region with each microelectrode individually driven and adapted to connect to single cell. Sugihara further fails to

show or suggest microelectrodes of the planar array configured to exclusively deliver current/voltage to the array region. To the contrary, Sugihara et al. discloses *measuring* cell potentials using all the microelectrodes. [2:64-67]. Absent any teaching, suggestion, or motivation to dedicate individual microelectrodes to a single cell and to configure the microelectrodes to deliver exclusively, current/voltage so as to perform electroporation of the individual cell, Sugihara et al. does not render claim 4 obvious alone, or in combination with Xu et al.

Johnson also fails to fill the deficiencies of Xu et al. and Sugihara. Johnson is directed to an electroporation apparatus to facilitate the controlled introduction of genes, drugs and chemicals into cells cultured on an array to allow rapid parallel analysis. [3:11-13]. The method is distinguished from prior art methods in that subpopulations of cells are loaded with one gene and other subpopulations are loaded with a different gene. [8:6-10]. Regions of the array are selectively electroporated to enable imaging techniques, e.g., fluorescent assays, to determine the cellular effects of the introduced substances. See generally, Col. 7, l. 28-Col. 8, l. 5.

Solutions carrying the genes, drugs, etc., are introduced into a perfusion chamber preferably having a transparent top to enable imaging analysis. [4:51-54]. The chamber contains all the cultured cells so that the entire population of cells is exposed to the solution in an indiscriminate manner. The electroporation process is achieved by applying an electric field across a cathode and an anode as shown in FIG. 2. [4:42-45]. The array is broken down into regions that are selectively electroporated. [4:51-56]. Thus, each array region has a least one cathode and at least one anode electrode, and the cells are electroporated based upon their location in a specific region of the chamber array. Each cell is in communication with at least

one cathode and at least one anode in the array region.

The electrodes are comprised of glass optical fiber bundles bonded with a biocompatible epoxy to form microwires. The microwires of the electrode protrude from the surface of the electrode and create spaces into which the cells migrate and adhere. This prevents the cells from being flushed away when solutions flow through the perfusion chamber. Multiple microwires are dedicated to each array unit cell or array region. See generally, Col. 6, l. 19-51. Based on this construction, each cell in an array region is exposed to, and in communication with multiple, variably-oriented microwires. Johnson does not disclose microelectrodes in a single planar array with each microelectrode dedicated to the delivery of current/voltage to the array region occupied by the planar array.

With respect to the orientation of the charged electrode to the reference electrode, Johnson describes reference electrodes within the same array region as the charged electrode, FIGS. 5A, 5B and 5C, or a large exterior reference electrode placed above all the array regions, FIG. 5D.

Johnson fails to fill the deficiencies of Xu on a number of grounds. As shown in FIG. 2, the charged electrode and the reference electrode are both connected to the same cell. As each cell can occupy only one array region, the charged and reference electrodes must be in the same array region. Applicants' invention has the reference electrode positioned outside the array region in a planar orientation to the microelectrodes.

Because of the very small size of the Johnson microwires, multiple microwires are energized or activated as Johnson does not disclose or suggest individual control of each microwire. Thus, multiple microwires in a bundle are activated together and communicate with each cell together. Each microwire is not dedicated

to a single cell and each cell does not have a single microwire dedicated to it. In the embodiment using a large reference electrode, Johnson does not disclose a reference electrode in a planar orientation relative to the array of microelectrodes.

Unlike Applicants' claimed invention and as absent in the Xu et al. disclosure, Johnson does not disclose a single microelectrode array in which each electrode is dedicated to a single cell and each dedicated to deliver exclusively current/voltage to the array region. Rather, the disclosed microwires are configured to perform different functions in the same array region.

For all these reasons, Johnson does not show or suggest Applicants' claimed invention alone, or in combination with Xu et al. and Sugihara. Accordingly, for all the foregoing reasons, Applicants respectfully request reconsideration and removal of the rejection of claim 4 under § 103(a).

Claims 5, 7-11 and 15 depend, directly or ultimately, from claim 4 and are allowable for the same reasons given for the allowability of claim 4. Accordingly, reconsideration and removal of the rejection of claims 5, 7-11 and 15 under § 103(a) are respectfully requested.

Claim 12 stands rejected under § 103(a) as being obvious over Xu et al. in view of Sugihara as applied to claim 11, and further in view of Casnig (US 5,134,070). Applicants respectfully traverse the rejection.

Claim 12 depends ultimately from claim 4 and is therefore allowable for the same reasons given for claim 4. As stated, claim 4 recites a single planar array of microelectrodes in which each microelectrode is individually driven and adapted to connect to single cell. All the microelectrodes of the array are configured for the delivery of current/voltage to the array region occupied by the planar array. Xu et al. and Sugihara do not show or suggest such a feature. Casnig is equally deficient for

the following reasons.

Casnig discloses a method and device for inducing electroporation of a monolayer of cells. The apparatus includes a Petri-like dish with an electrically-conductive substrate on which the cells are grown. At least one electrode attached to a bottom surface of the substrate provides a conduit for the introduction of electric current to perform the electroporation. Based on the apparatus and method disclosed, the opposing and detection electrodes of Casnig facilitate electroporation, and detection of the effects of electroporation, in a plural, nondiscriminatory manner-all cells are treated as a group or colony rather than on an individual basis. *See generally* Summary of the Invention [3:36-4:19]

Casnig does not disclose, or even suggest, a planar array of microelectrodes, each microelectrode individually driven and dedicated to a single cell. To the contrary, Casnig discloses measuring cell potentials as a group using detector microelectrodes. [4:16-19]. Moreover, Casnig does not disclose a single planar array of microelectrodes wherein each microelectrode is configured to deliver exclusively current/voltage to the array region occupied by the planar array. Absent any teaching, suggestion, or motivation to construct a single planar array of microelectrodes with each microelectrode selectively driven and adapted for connection to a single cell so as to perform electroporation of the individual cell, and absent any teaching, suggestion, or motivation to configure the microelectrodes to deliver exclusively current/voltage to the array region, Casnig does not render claim 12 obvious alone, or in combination with Xu et al. in view of Sugihara. Accordingly, for all the foregoing reasons, Applicants again respectfully request reconsideration and removal of the rejection of claim 12 under § 103(a).

Claims 13 and 14 stand rejected under § 103(a) as being obvious over Xu et

al. in view of Sugihara as applied to claim 11, and further in view of Gomez et al. (US 2003/0157587). Applicants respectfully traverse the rejection.

Claims 13 and 14 depend ultimately from claim 4 and are allowable for the same reasons as those given in support of claim 4. As stated, the microelectrodes recited in claim 4 are organized in a single planar array and are each connected to a single cell and selectively driven to perform electroporation of a single cell. All of the microelectrodes of the planar array are configured to deliver exclusively current/voltage to the array regions occupied by the array. Neither Xu et al. nor Sugihara show or suggest such features. Gomez et al. is equally deficient for the following reasons.

Gomez et al. discloses a method and biochip for collecting a microbiological entity of interest with a non-uniform electric field created by electrically pulsing electrodes in a collection chamber to capture the specimen via dielectrophoresis. Collection electrodes deliver the electric current to capture the desired microbiological entity and may also perform a detection function. In an alternative embodiment, dedicated detection electrodes may be placed in the containment chamber. [0036]. Similar to the other cited references, Gomez et al. does not disclose a single planar array of microelectrodes in which each electrode is adapted for connection to a single cell and each electrode is configured to deliver exclusively current/voltage to the array region occupied by the array. Apart from these glaring deficiencies, it should also be noted Gomez et al. is not directed to electroporation and should not be considered analogous art.

Gomez et al. does not disclose, or even suggest, the construction of a single planar array of microelectrodes, each dedicated to individual cells or molecules, and each configured to deliver exclusively current/voltage to the array region. To the

contrary, Gomez et al. discloses collection and/or detection electrodes that measure microbiological entities as a group. In fact, Gomez et al. describes using a carrier element disposed on the collection electrodes to entrain the microbiological species and concentrate it at the point of measurement. [0034-0035]. Therefore, Gomez et al. teaches the collection of multiple cells or molecules on a single electrode, which teaches away from Applicants' claimed invention.

Absent any teaching, suggestion, or motivation to construct a single planar array of microelectrodes in which each microelectrode is adapted for connection to a single cell so as to perform electroporation of the individual cell, and in which each microelectrode is configured to deliver exclusively current/voltage to the array region, Gomez et al. does not render claims 13 and 14 obvious alone, or in combination with Xu et al. in view of Sugihara. Accordingly, for all the foregoing reasons, Applicants respectfully request reconsideration and removal of the rejections of claims 13 and 14 under § 103(a).

Claim 12 stands rejected under § 103(a) as being obvious over Xu et al. in view of Sugihara and Johnson as applied to claim 11, and further in view of Casnig (US 5,134,070). Applicants respectfully traverse the rejection.

To reiterate, claim 12 depends ultimately from claim 4 and is therefore allowable for the same reasons given for claim 4. As stated, claim 4 recites a single planar array of microelectrodes in which each microelectrode is individually driven and adapted to connect to single cell, and each microelectrode is configured to deliver exclusively current/voltage to the array region occupied by the array. Xu et al., Sugihara and Johnson do not show or suggest such features. Casnig is equally deficient for the following reasons.

As previously stated, Casnig discloses a method and device for inducing

electroporation of a monolayer of cells. The apparatus includes a Petri-like dish with an electrically-conductive substrate on which the cells are grown. At least one electrode attached to a bottom surface of the substrate provides a conduit for the introduction of electric current to perform the electroporation. Based on the apparatus and method disclosed, the opposing and detection electrodes of Casnig facilitate electroporation, and detection of the effects of electroporation, in a plural, nondiscriminatory manner-all cells are treated as a group or colony rather than on an individual basis. *See generally* Summary of the Invention [3:36-4:19]

Casnig does not disclose, or even suggest, a single planar array of microelectrodes, each microelectrode dedicated to a single cell and each microelectrode configured to deliver exclusively current/voltage to the array region occupied by the array. To the contrary, Casnig discloses measuring cell potentials as a group using detector microelectrodes combined with current/voltage delivery electrodes. [4:16-19]. Absent any teaching, suggestion, or motivation to construct a single planar array of microelectrodes in an array region with each microelectrode selectively driven and adapted for connection to a single cell so as to perform electroporation of the individual cell, and wherein each microelectrode is configured to delivery exclusively current/voltage to the array region, Casnig does not render claim 12 obvious alone, or in combination with Xu et al., Sugihara and Johnson. Accordingly, for all the foregoing reasons, Applicants again respectfully request reconsideration and removal of the rejection of claim 12 under § 103(a).

Claims 13 and 14 stand rejected under § 103(a) as being obvious over Xu et al. in view of Sugihara and Johnson as applied to claim 11, and further in view of Gomez et al. (US 2003/0157587). Applicants respectfully traverse the rejection.

As stated herein, claims 13 and 14 depend ultimately from claim 4 and are

allowable for the same reasons as those given in support of claim 4. Microelectrodes recited in claim 4 are organized in a single planar array and are each connected to a single cell and selectively driven to perform electroporation of a single cell. Each microelectrode is configured to deliver exclusively current/voltage to the array region occupied by the planar array. None of the Xu et al., Sugihara and Johnson references show or suggest such features. Gomez et al. is equally deficient for the following reasons.

Gomez et al. discloses a method and biochip for collecting a microbiological entity of interest with a non-uniform electric field created by electrically pulsing electrodes in a collection chamber to capture the specimen via dielectrophoresis. Collection electrodes deliver the electric current to capture the desired microbiological entity and may also perform a detection function. In an alternative embodiment, dedicated detection electrodes may be placed in the containment chamber. [0036]. Similar to the other cited references, Gomez et al. does not disclose a single planar array of microelectrodes in which each electrode is adapted for connection to a single cell and each microelectrode is configured to deliver exclusively current/voltage to the array region occupied by the array. Apart from these glaring deficiencies, it should also be noted Gomez et al. is not directed to electroporation and should not be considered analogous art.

Gomez et al. does not disclose, or even suggest, the construction of a single planar array of microelectrodes, each dedicated to individual cells or molecules. Gomez et al. further does not disclose that all the microelectrodes are configured to deliver exclusively current/voltage to the array region occupied by the array. To the contrary, Gomez et al. discloses collection and/or detection electrodes that measure microbiological entities as a group. In fact, Gomez et al. describes using a carrier

element disposed on the collection electrodes to entrain the microbiological species and concentrate it at the point of measurement. [0034-0035]. Therefore, Gomez et al. teaches the collection of multiple cells or molecules on a single electrode, which teaches away from Applicants' claimed invention.

Absent any teaching, suggestion, or motivation to construct a single planar array of microelectrodes in which each microelectrode is adapted for connection to a single cell so as to perform electroporation of the individual cell, and wherein each microelectrode is configured to deliver exclusively current/voltage to the array region occupied by the array, Gomez et al. does not render claims 13 and 14 obvious alone, or in combination with Xu et al., Sugihara and Johnson. Accordingly, for all the foregoing reasons, Applicants respectfully request reconsideration and removal of the rejections of claims 13 and 14 under § 103(a).

VI. Conclusion:

For all the foregoing reasons, the claims are considered to define patentably over the prior art. Reconsideration is requested and favorable action is solicited.

Respectfully Submitted,

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Dated: April 8, 2011.

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